EXHIBIT G

Applicants: Arlindo L. Castelhano et al.
Serial No. 10/816,329
Filed: March 31, 2004

Dkt. No. 60390-AZ-PCT-US/JPW/GJG/NDP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Arlindo L. Castelhano et al.	
Serial No.	:	10/816,329	Examiner: T. McKenzie
Filed	:	March 31, 2004	Group Art Unit: 1624
For	:	4-HETEROCYCLO-PYRROLO[2,3d] PYRIMIDINE COMPOSITIONS AND THEIR USE	

1185 Avenue of the Americas
New York, New York 10036

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO MAY 17, 2005 OFFICE ACTION AND SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

This Amendment is submitted in response to a May 17, 2005 Office Action issued by the United States Patent and Trademark Office in connection with the above-identified application. A Notice of Abandonment was issued March 17, 2006 in the subject application. Accordingly, this Amendment accompanies a Petition to Revive an Unintentionally Abandoned Application under 37 C.F.R. §1.137(b).

Please amend the subject application as follows:

Amendments to the Specification

Please amend the specification on page 1, line 1 as follows:

-- This application is a divisional of U.S. Application No. 09/728,229, filed December 1, 2000, now ~~allowed~~Patent No. 6,800,633, which is a continuation of PCT International Application No. PCT/US99/12135, filed June 1, 1999, designating the United States of America, which is a continuation-in-part and claims priority of U.S. Provisional Application No. 60/087,702, filed June 2, 1998, U.S. Provisional Application No. 60/123,216, filed March 8, 1999 and U.S. Provisional Application No. 60/126,527, filed March 26, 1999 the contents of which are hereby incorporated by reference. --

Please amend the title of the subject application as follows:

-- 4-HETEROCYCLO-PYRROLO [2,3d] PYRIMIDINE COMPOSITIONS AND THEIR USE --

Remarks

Claims 5, 11, 12, 22, 23 and 187-189 are pending in the subject application.

Priority

On page 2 of the May 17, 2005 Office Action, the Examiner requested that the status of non-provisional parent application should be included in the specification.

In response, Applicants have amended page 1, line 1 of the subject disclosure in order to include the status of non-provisional parent application. Accordingly, Applicants respectfully request that the Examiner withdraw this objection to the specification.

Title

On page 2 of the May 17, 2005 Office Action, the Examiner objected to the title of the invention as no longer descriptive after restriction.

In response, Applicants have amended the title of the invention by adding the phrase "4-Heterocyclo-" before the word "Pyrrolo", as Examiner suggested. Accordingly, Applicants respectfully request that the Examiner withdraw this objection to the specification.

Abstract

On page 2 of the May 17, 2005 Office Action, the Examiner objected to the abstract of the subject application as too short and generic. The Examiner suggested claim 11, including the figure and the utility.

In response, Applicants point out that the Abstract was amended by the Preliminary Amendment (see pages 6-7), submitted March 31, 2004, in order to reflect claim 11, including the figure and the utility. Accordingly, Applicants respectfully request that the Examiner withdraw this objection to the specification.

Rejection Under 35 U.S.C. §112, first paragraph

On pages 3-6 of the May 17, 2005 Official Action, the Examiner rejected claim 5 under 35 U.S.C. 112, first paragraph, alleging that the specification does not reasonably provide enablement for treating any human disease. In support of this rejection, the Examiner set forth five main issues:

1) the lack of any correlation between clinical efficacy for treatment of the twelve diseases and Applicants' four *in vitro* assay;
2) the limited biological testing done upon compounds within the scope of formula (I);
3) the state of the prior art;
4) the complete lack of skill of clinicians in using A1 agonists in treating disease; and
5) the breadth of the claims.

Applicants' Reply

Items 1 and 2

In response to items 1) and 2), Applicants point out that "correlation" refers to the relationship between *in vitro* animal model assays and a claimed method of use. M.P.E.P.

§2164.02. A rigorous or an invariable exact correlation is not required. *Id.*, *citing* Cross v. Iizuka, 753 F.2d 1040 (Fed.Cir. 1985).

The *in vitro* assays to which Examiner refers on page 4 of the May 17, 2005 Office Action are radioligand binding assays. Data from radioligand binding assays is an accepted means to correlate a compound to its use. See, e.g., Section 1.3 entitled *In vitro* Test Systems of Yan, Expert Opinion on Emerging Drugs, which states that:

> "[Adenosine receptors] and their ligands may be investigated in binding and functional assays. Radioligand binding assays can be conducted easily and fast; the data directly reflect the interaction of a compound with the receptor protein without uncontrollable intermediate steps."

The radioligand binding assay data for Applicants' compounds directly reflects the interaction of the compounds with adenosine receptors. Such interaction is known to correlate to the indications listed in claim 5 in a subject. In support, Applicants direct the Examiner's attention to the following references, each of which correlates an interaction with an indication recited in claim 5:

1. Marx, D. et al., *Drug News Perspect.* (2001), 14(2): 89-100 (Exhibit 104 of March 31, 2004 Information Disclosure Statement). The reference discloses adenosine receptor antagonists for the treatment of mast cell degranulation, bronchoconstriction, neutrophil chemotaxis and asthma.

2. Knutsen et al., *Current Opinion in Investigational Drugs* (2001), 2(5): 668-673, a copy of which is attached as **Exhibit 19** in the enclosed Second Supplemental Information Disclosure Statement. The reference discloses the use of A2a adenosine receptor antagonist KW-6002 for the treatment of Parkinson's disease. Of particular note, KW-6002 is in Phase II clinical trials for the treatment of Parkinson's disease;

3. Szkotak, A.J. et al., *Am. J. Physiol. Cell Physiol.* (2001), 281: C1991-C2002, a copy of which is attached as **Exhibit 28** in the enclosed Second Supplemental Information Disclosure Statement. The reference describes how the A1 adenosine receptor affects respiratory epithelia;

4. Phillis, J.W. *Brain Research* (1995), 705:79-84, a copy of which is attached as **Exhibit 24** in the enclosed Second Supplemental Information Disclosure Statement. The reference discloses the use of A2a adenosine receptor antagonists in prevention of cerebral injuries resulting from stroke or cardiac arrest (i.e. cerebral ischemia);

5. Welch, W.J. *Expert Opin. Investig. Drugs* (2002), 11(11): 1553-1562, a copy of which is attached as **Exhibit 30** in the enclosed Second Supplemental Information Disclosure Statement. The reference discloses the use of A1 adenosine receptor antagonists for use as a diuretic agent (i.e. antidiuresis); and

6. Avila M.Y. et al., *Br. J. Pharmacol.* (2001) 134:241-245, a copy of which is attached as **Exhibit 6** in the enclosed Second

Supplemental Information Disclosure Statement. The reference discloses the use of A2a receptor antagonists for decreasing intraocular pressure (i.e. glaucoma).

As such, Applicants contend that the necessary correlation exists between the compounds and their uses for treatment of the indications listed in claim 5 based on Applicants' *in vitro* assays.

Items 3 and 4

In response to items 3) and 4), Applicants contend that Examiner misrepresents Yan's Expert Opinion on Emerging Drugs. Tempering the Examiner's summary of Yan on page 5 of the May 17, 2005 Office Action, Yan also states in the same paragraph summarized by Examiner:

> "Partial [A1-selective] agonists may be advantageous, especially for non-cardiovascular indications, and are currently in preclinical development."
>
> "A2a agonists are anti-inflammatory agents."
>
> "A3-selective agonists have been described as promising cardio- and cerebro-protective agents."

The following more definitive statements made within the body of Yan's Expert Opinion provide additional insight on the state of the art:

> "Full agonists of A1 receptors depress the [central nervous system] and the heart and have numerous peripheral effects." (pg. 545)
>
> "A2b agonists can inhibit fibroblast and smooth muscle proliferation." (pg. 549)
>
> "A3 agonists have been shown to exhibit cardioprotective properties." (pg. 553)

Similarly, the following statements made in the body of Baraldi's (1999) Expert Opinion contradict Examiner's assertion regarding the clarity of the effects of A3 receptor agonists:

> "By regulating cell death, A3 receptors could play a fundamental role in human disease. This relationship between A3 receptor and apoptosis suggests that A3 ligands could be useful in the treatment of diseases in which cytoxicity is undesirable, such as neurodegenerative disorders, cancer, inflammation, asthma, etc." (pg. 525)
>
> "Furthermore, selective activation of A3 receptors appears to inhibit human neutrophil degranulation, suggesting the anti-inflammatory potential of A3 agonists in neutrophil-mediated tissue injury." (pg. 525)

As such, Applicants maintain that the state of the prior art, including the skill of clinicians in using A1 agonists in treating disease, is sufficient to teach one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

In view of the preceding discussion, applicants contend that claim 5 is enabled. Consequently, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Item 5

In response to item 5), Applicants point out that formula (I) of claim 5 denotes a genus of compounds, which genus is sufficiently described by a representative number of species and sufficient to show the Applicants were in possession of the claimed genus. M.P.E.P. §2163(II)(A)(3)(a)(ii). Examiner has acknowledged that there is data on compounds found in pages 109-124, all of which are defined by their structure, and all of which may be reduced to practice utilizing methods disclosed in the subject specification. As such, the scope of the claims is not broad.

Applicants also point out that, contrary to the Examiner's assertion, one of reasonable skill in the art would recognize "neutrophil chemotaxis" to represent a finite number of diseases typified by an inflammatory response, e.g., asthma. In fact, "neutrophil chemotaxis" connotes an inflammatory response. See, e.g., Rennard, B.O. et al., Chicken Soup

Inhibits Neutrophil Chemotaxis *In Vitro*, Chest (2000) 118:1150-1157, found at http://www.chestjournal.org/cgi/content/full/118/4/1150: "[A]nother potential mechanism for beneficial effects could be an attenuation of the inflammatory response. In order to evaluate that possibility, the ability of [agent] to inhibit neutrophil chemotaxis in response to standard chemotactic stimuli was evaluated and demonstrated in the current study." As such, "neutrophil chemotaxis" is not broad.

Double Patenting

On page 6 of the May 17, 2005 Official Action, the Examiner rejected claims 5, 11, 12, 23 and 187-189 under the doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 3, 4-5, 8, 9, 12, 29 and 33 of U.S. Patent No. 6,664,252.

On page 8 of the May 17, 2005 Official Action, the Examiner rejected claims 5, 11, 12, 23 and 187-189 under the doctrine of obviousness-type double patenting as being unpatentable over claims 1, 9, 10, 14, 16, 29-31 and 35-37 of U.S. Patent No. 6,680,324.

On page 8 of the May 17, 2005 Official Action, the Examiner rejected claims 5, 11, 12 and 187-189 under the doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 11-14 and 16 of U.S. Patent No. 6,800,633.

In response, Applicants attach hereto as **Exhibit A** a Terminal Disclaimer which disclaims the terminal portion of the

statutory term of any patent granted on the subject application which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §154 to §156 and §173 of commonly assigned U.S. Patent Nos. 6,664,252, 6,680,324 and 6,800,633. Accordingly, the double patenting rejection is moot with respect to U.S. Patent Nos. 6,664,252, 6,680,324 and 6,800,633.

Under 37 C.F.R. §1.321(b), a terminal disclaimer must be accompanied by the fee set forth in 37 C.F.R. §1.20(d). Under 37 C.F.R. §1.20(d), the fee for filing a terminal disclaimer is ONE HUNDRED THIRTY DOLLARS ($130.00) and a check including this amount is enclosed.

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following document which is listed on Form PTO-1449 (**Exhibit B**) and is also listed below.

This Information Disclosure Statement is being submitted pursuant to 37 C.F.R. §1.97(c) after the mailing of a first Office Action on the merits. The fee for an Information Disclosure Statement under 37 C.F.R. §1.97(c) as set forth in 37 C.F.R. §1.17(p) for a large entity is $180.00 and a check including this amount is enclosed. Thus, this Information Disclosure Statement should be entered and considered.

Pursuant to the Notice appearing in the August 5, 2003 Official Gazette, because this application was filed after June 30, 2003, a copy of the U.S. Patent Application listed herein is not provided.

1. U.S. Patent No. 5,208,240, issued May 4, 1993, Peet et al.;

2. U.S. Patent No. 5,296,484, issued March 22, 1994, Coghlan et al.;

3. U.S. Patent No. 5,877,180, issued March 2, 1999, Linden et al.;

4. U.S. Patent No. 5,935,964, issued August 10, 1999, Baraldi et al.;

5. PCT International Application No. WO 94/19349, published September 1, 1994 **(Exhibit 1)**;

6. PCT International Application No. WO 97/02266, published January 23, 1997 **(Exhibit 2)**;

7. PCT International Application No. WO 98/29397, published July 9, 1998 **(Exhibit 3)**;

8. Abbracchio, M. et al. (1999) "Brain Adenosine Receptors and Targets for Therapeutic Intervention in Neurodegenerative Disease" Ann. NY. Acad. Sci. 890:79-92 **(Exhibit 4)**;

9. Aoyama S. et al. (2000) "Rescue of Locomotor Impairment in Dopamine D2 Receptor-Deficient Mice by an Adenosine A2a Receptor Antagonist" J. Neuroscience 20(15):5848-5852 **(Exhibit 5)**;

10. Avila, M.Y. (2001) "A1-A2a and A3-Subtype Adenosine receptors Modulate Intraocular Pressure in the Mouse" J. of Pharmacol. 241-245 **(Exhibit 6)**;

11. Baraldi, P.G. et al. (1996) "Pyrazolo [4,3-e]-1,2,4 triazolo [1,5-c]pyrimidine Derivatives: Potent and Selective A2a Adenosine Antagonists" J. Med. Chem. 39:1164-1171 **(Exhibit 7)**;

12. Barrett, R.J. et al. (1992) "N-0861 Selectively Antagonizes Adenosine A1 Receptors *in vivo*" European J. Pharmacology 216:9-16 **(Exhibit 8)**;

13. Campbell, R.M. et al. (1999) "Selective A1-Adenosine Receptor Antagonists Identified using Yeast *Saccharomycces Cerevisiae* Functional Assays" Bioorg. & Med. Chem. Lett. 9(16):2413-2418 **(Exhibit 9)**;

14. Coney, A.M. et al. (1998) "Role of Adenosine and its Receptors in the Vasodilation Induced in the Cerebral Cortex of the Rat by Systemic Hypoxia" J. Physiol. 509:507-518 **(Exhibit 10)**;

15. Cooper, J.A. (1995) "Adenosine Receptor-induced Cyclic AMP Generation and Inhibition of 5-hydroxytryptamine release in Human Platelets" Br. J. Clin. Pharmacol. 40:43-50 **(Exhibit 11)**;

16. Cummings, J. et al. (2000) "Antagonism of the Cardiodepressant Effects of Adenosine During Acute Hypoxia" Academic Emergency Medicine 7(8):618-624 **(Exhibit 12)**;

17. Dhainuat, A. et al. (1996) "New Purines and Purine Analogs as Modulators of Multidrug Resistance" J. Med. Chem. 39:4099-4108 **(Exhibit 13)**;

18. Gao, E. et al. (2001) "Adenosine A1 Receptor Antagonist Prolongs Survival in the Hypoxic Rat" J. Cardiovascular Pharm. 38:384-394 **(Exhibit 14)**;

19. Ghiardi, G.J. et al. (1999) "The Purine Nucleoside Adenosine in Retinal Ischemia-Reperfusion Injury" Vision

Research 39:2519-2535 **(Exhibit 15)**;

20. Li, J.M. et al. (1998) "Adenosine A2a Receptors Increase Arterial Endothelial Cell Nitric Oxide" J. Surg. Res. 80:357-364 **(Exhibit 16)**;

21. Kanda, T. et al. (1998) "Adenosine A2a Receptors Modify Motor Function in MPTP-treated Common Marmosets" Neuroreport 9:2857-2860 **(Exhibit 17)**;

22. Kanda, T. et al. (2000) "Combined Use of the Adenosine A2a Antagonist KW-6002 with L-DOPA or with Selective D1 or D2 Dopamine Agonists Increases Antiparkinsonian Activity but not Dyskensia in MPTP-Treated Monkeys" Experimental Neurology 162:321-327 **(Exhibit 18)**;

23. Knutsen, L.J.S. et al. (2001) Curr. Opin. Invest. Drugs 2(5):668-673 **(Exhibit 19)**;

24. Kopf, S.R. et al. (1999) "Adenosine and Memory Storage: Effect of A1 and A2 Receptor Antagonists" Psychopharmacology 146:214-219 **(Exhibit 20)**;

25. Montesinos, M.C. et al. (2002) "Adenosine Promotes Wounds Healings and Mediates Angiogenesis in Response to Tissue Injury Via Occupancy of A2a Receptors" American Journal of Pathology 160(6):2009-2018 **(Exhibit 21)**;

26. Nishiyama, A. (1999) "Adenosine A1 Receptor Antagonists KW-3902 Prevents Hypoxia-Induced Renal Vasoconstriction" J. Pharm. Exp. Ther. 291:988-993 **(Exhibit 22)**;

27. Nishiyama, A. et al. (2001) "Interactions of Adenosine A1 and A2a Receptors on Renal Microvascular Reactivity" Am. J. Physiol. Renal Physiol. 280:F406-F414 **(Exhibit 23)**;

28. Phillis, J.W. (1995) "The Effects of Selective A1 and A2a Adenosine Receptor Antagonists on Cerebral Ischemic Injury in the Gerbil" Brain Research 705:79-84 **(Exhibit 24)**;

29. Taomoto, M. ety al. (2000) "Localization of Adenosine A2a Receptor in Retinal Development and Oxygen-Induced Retinopathy" Investigative Ophthalmology & Visual Science 41(1):230-243 **(Exhibit 25)**;

30. Shiozaki, S. et al. (1999) "Actions of Adenosine A2a Receptor Antagonist KW-6002 on Drug-induced Catalepsy and Hypokinesia Caused by Reserpine of MPTP" Psychopharmacology 147:90-95 **(Exhibit 26)**;

31. Svenningsson, P. et al. (1999) "Distribution, Biochemistry and Function of Striatal Adenosine A2a Receptors" Prog. Neurobiol. 59(4):355-396 **(Exhibit 27)**;

32. Szkotak, A.J. et al. 2001) "Regulation of K+ Current in Human Airway Epithelial Cells by Exogenous and Autocrine Adenosine" Am. J. Physiol. Cell Physiol. 281:C1991-C2002 **(Exhibit 28)**;

33. Varani, K. et al. (1998) "[^{3}H]-SCH 58261 Labelling of Functional A2a Adenosine Receptors in Human Neutrophil Membranes" Br. J. Pharmacol. 123:1723-1731 **(Exhibit 29)**;

34. Welch, W.J. (2002) "Adenosine Type 1 Receptor Antagonists in Fluid Retaining Disorders" Expert Opin. Investig. Drugs 11(11):1553-1562 **(Exhibit 30)**; and

35. Zhao, Z. et al. (1996) "Bioactivation of 6,7-Dimethyl-2,4-di-1-pyrrolidinyl-7H-pyrrolo[2,3-d]pyrimidine (U-89843) to Reactive Intermediates that Bind Covalently to Macromolecules and Produce Genotoxicity" Chem. Res. Toxicol. 9:1230-1239 **(Exhibit 31)**;

Applicants request that the Examiner review the reference and make it of record in the subject application.

Summary

In view of the amendments and remarks set forth above, applicant maintains that the grounds of the Examiner's rejections and objections set forth in the May 17, 2005 Office Action have been overcome. Applicant respectfully requests that the Examiner reconsider and withdraw these grounds of rejection and objection, and solicit allowance of the claims now pending.

If a telephone interview would be of assistance in resolving any issue in connection with this petition, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $130.00 terminal disclaimer fee as set forth in 37 C.F.R. §1.20(d) and $180.00 information disclosure statement fee as set forth in 37 C.F.R. §1.17(p), is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents Washington, DC 22313.

Gary J. Gershik 5/16/06

John P. White Date
Reg. No. 28,678
Gary J. Gershik
Reg. No. 39,992

John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

EXHIBIT A

Applicants: Arlindo L. Castelhano et al.
Serial No. 10/816,329
Filed: March 31, 2004

Dkt. No. 60390-AZ-PCT-US/JPW/GJG/NDP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Arlindo L. Castelhano et al.	
Serial No.	:	10/816,329	Examiner: T. McKenzie
Filed	:	March 31, 2004	Group Art Unit: 1624
For	:	4-HETEROCYCLO-PYRROLO [2,3d] PYRIMIDINE COMPOSITIONS AND THEIR USE	

1185 Avenue of the Americas
New York, New York 10036

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

TERMINAL DISCLAIMER

Petitioner OSI Pharmaceuticals, Inc., having a place of business at 41 Pinelawn Road, Melville, NY 11747, the sole assignee of record of the entire right, title, and interest in and to the above-identified application by virtue of an Assignment from Arlindo L. Castelhano, Bryan McKibben and David J. Witter, recorded with the United States Patent and Trademark Office on March 26, 2001 at Reel 011704, Frames 0888-0892, a copy of which is attached hereto as **Exhibit 1**, hereby disclaims, except as provided below, the terminal portion of the statutory term of any patent granted on the subject application which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §154 to §156 and §173 of commonly assigned U.S. Patent Nos. 6,664,252, 6,680,324 and 6,800,633.

Petitioner hereby agrees that any patent granted on the subject application shall be enforceable only for and during such period that U.S. Patent Nos. 6,664,252, 6,680,324 and 6,800,633 are commonly owned and that this agreement will run with any patent granted on the subject application and be binding upon the grantee, its successors and assigns.

Applicants: Arlindo L. Castelhano et al.
Serial No.: 10/816,329
Filed: March 31, 2004
Exhibit A

In making the above disclaimer, Petitioner does not disclaim the terminal portion of any patent granted on the subject application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §154 to §156 and §173 of U.S. Patent Nos. 6,664,252, 6,680,324 and 6,800,633 in the event that such patent later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. §1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term.

I certify that I have reviewed the attached Assignment, and that, to the best of my knowledge and belief, OSI Pharmaceuticals, Inc.. have the entire right, title and interest in and to the subject application. I further certify that I am authorized to sign this Terminal Disclaimer on behalf of OSI Pharmaceuticals, Inc. as indicated.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

OSI PHARMACEUTICALS, INC.

Date: Jan 25, 2007 By: Barbara A. Wood

Barbara A. Wood, Esq.
Vice President and General Counsel

EXHIBIT 1

Applicants: Arlindo L. Castelhano et al.
Serial No. 10/816,329
Filed: March 31, 2004

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JULY 02, 2001

PTAS

101685534A

COOPER & DUNHAM LLP
JOHN P. WHITE, ESQ.
1185 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 03/26/2001 REEL/FRAME: 011704/0888
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
CASTELHANO, ARLINDO L. DOC DATE: 02/06/2001

ASSIGNOR:
MCKIBBEN, BRYAN DOC DATE: 02/05/2001

ASSIGNOR:
WITTER, DAVID J. DOC DATE: 02/05/2001

ASSIGNEE:
OSI PHARMACEUTICALS, INC.
106 LINDBERGH BLVD.
UNIONDALE, NEW YORK 11553-3649

SERIAL NUMBER: 09728229 FILING DATE: 12/01/2000
PATENT NUMBER: ISSUE DATE:

Applicants: Arlindo L. Castelhano et al.
Serial No.: 10/816,329
Filed: March 31, 2004
Exhibit 1

011704/0888 PAGE 2

MARY BENTON, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

04-26-2001

Docket No. 1919/60390-A-PCT-US
JPW/GJG/CMR

101685534

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

To the Assistant Secretary and Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Arlindo L. Castelhano
Bryan McKibben
David J. Witter
3.26.01

Additional name(s) of conveying party(ies) attached?
☐ Yes ☒ No

2. Name and address of receiving party(ies):
Name: OSI PHARMACEUTICALS, INC.
Internal Address:
Street Address: 106 Lindbergh Blvd.
City/State/Zip: Uniondale, N.Y., 11553-3649

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of Conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other

Execution Date(s): 2/6/01, 2/5/01, 2/5/01

4. Application number(s) or patent number(s): If this document is being filed together with a new application, the execution date(s) of the application is(are):

A. Patent Application No.(s) 09/728,229
Filed: 12/1/00

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: John P. White, Esq.
Internal Address:
Street Address: Cooper & Dunham LLP
1185 Avenue of the Americas
City/State/Zip: New York, New York 10036

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR §3.41): ..... $ 40.00
☐ Enclosed
☒ Authorized to be charged to deposit account

8. Deposit account number:
03-3125

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

John P. White — Name of Person Signing
Signature
March 21, 2001 — Date

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date
John P. White
Registration No. 28,678

Total Number of pages including cover sheet, attachments and document: 4

OMB No. 0651-0011 (exp. 4/94)

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

Assignment

In consideration of One Dollar ($1.00), and other good and valuable considerations, the receipt of which is hereby acknowledged, I , the undersigned, Arlindo L. Castelhano residing at 3 Eagle Court, New City, New York 10579, USA; Bryan McKibben residing at Apartment 8, 15 Greenridge Avenue, White Plains, New York 10605, USA; and David J. Witter residing at 12 Arbutus Road, Putnam Valley, New York 10579, USA

Hereby sell, assign and transfer to OSI Pharmaceuticals, Inc. a corporation of the State of New York having a place of business at 106 Charles Lindbergh Blvd. in the County of Nassau and State of New York 11553-3649 its successors, assigns and legal representatives, the entire right, title and interest for all countries, in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed, in the application for United States Patent, which has been executed by the undersigned February 6, 2001 and is entitled February 5, 2001 February 5, 2001

PYRROLO[2,3d]PYRIMIDINE COMPOSITIONS AND THEIR USE

(U.S. Serial No. 09/728,229 Filed December 1, 2000, a continuation of PCT International Application No. PCT/US99/12135, filed June 1, 1999 claiming priority of U.S. Provisional Application No. 60/087,702, filed June 2, 1998, U.S. Provisional Application No. 60/123,216, filed March 8, 1999 and U.S. Provisional Application No. 60/126,527, filed March 26, 1999)

and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for U.S. Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

Authorize and request the Commissioner of Patents of the United States to issue to said Assignee, the corporation above named, its successors, assigns and legal representatives, in accordance with this assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;

Agree that said Assignee may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; and that, when requested, without charge to, but at the expense of, said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigned's executors or administrators will, for the United States and all foreign countries execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignee, its successors, assigns and representatives, all facts known and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignee, its successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all patents on said inventions, in said Assignee, its successors, assigns and legal representatives; and

Covenant *with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.*

Arlindo L. Castelhano [L.S.]

Arlindo L. Castelhano

Date: Feb. 6, 2007 20

Witness: Sharon Norbeck

Sharon Norbeck

1799 Lockwood Rd

Mohegan Lake NY 10547

Bryan McK [L.S.]

Bryan McKibben

Date: Feb 5 20 07

Witness: Sharon Norbeck

Sharon Norbeck

1799 Lockwood Road

Mohegan Lake NY 10547

David J. Witter [L.S.]

Date: Feb 5 2001 David J. Witter

Witness: Shawn Norbeck
SHAWN NORBECK
1799 Lockwood Rd
Mohegan Lake NY 10547

ASSIGNMENT
BY

ARLINDO L. CASTELHANO
BRYAN MCKIBBEN
DAVID J. WITTER

TO

OSI PHARMACEUTICALS, INC.

Application for Letters Patent of the United States for:

PYRROLO[2,3d] PYRIMIDINE COMPOSITIONS AND THEIR USE

Attorney for John P. White

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, N.Y. 10036
212-278-0400

EXHIBIT B

Applicants: Arlindo L. Castelhano et al.
Serial No. 10/816,329
Filed: March 31, 2004

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 60390-AZ-PCT-US/JPW/GJG/NPD	Serial No. 10/816,329
INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)		Applicants: Arlindo L. Castelhano, et al.	
		Filing Date March 31, 2004	Group

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
	US	5 2 0 8 2 4 0	5/4/93	Peet et al.			
	US	5 2 9 6 4 8 4	3/22/94	Coghlan et al.			
	US	5 8 7 7 1 8 0	3/2/99	Linden et al.			
	US	5 9 3 5 9 6 4	8/10/99	Baraldi et al.			

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
	WO	9 4 1 9 3 4 9	9/1/94	PCT				
	WO	9 7 0 2 2 6 6	1/23/97	PCT				
	WO	9 8 2 9 3 9 7	7/9/98	PCT				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Abbracchio, M. et al. (1999) "Brain Adenosine Receptors and Targets for Therapeutic Intervention in Neurodegenerative Disease" Ann. NY. Acad. Sci. 890:79-92
		Aoyama S. et al. (2000) "Rescue of Locomotor Impairment in Dopamine D2 Receptor-Deficient Mice by an Adenosine A2a Receptor Antagonist" J. Neuroscience 20(15):5848-5852
		Avila, M.Y. (2001) "A1-A2a and A3-Subtype Adenosine receptors Modulate Intraocular Pressure in the Mouse" J. of Pharmacol. 241-245
		Baraldi, P.G. et al. (1996) "Pyrazolo [4,3-e]-1,2,4 triazolo [1,5-c]pyrimidine Derivatives: Potent and Selective A2a Adenosine Antagonists" J. Med. Chem. 39:1164-1171
		Barrett, R.J. et al. (1992) "N-0861 Selectively Antagonizes Adenosine A1 Receptors *in vivo*" European J. Pharmacology 216:9-16
		Campbell, R.M. et al. (1999) "Selective A1-Adenosine Receptor Antagonists Identified using Yeast *Saccharomyces Cerevisiae* Functional Assays" Bioorg. & Med. Chem. Lett. 9(16):2413-2418
		Coney, A.M. et al. (1998) "Role of Adenosine and its Receptors in the Vasodilation Induced in the Cerebral Cortex of the Rat by Systemic Hypoxia" J. Physiol. 509:507-518
		Cooper, J.A. (1995) "Adenosine Receptor-induced Cyclic AMP Generation and Inhibition of 5-hydroxytryptamine release in Human Platelets" Br. J. Clin. Pharmacol. 40:43-50
		Cummings, J. et al. (2000) "Antagonism of the Cardiodepressant Effects of Adenosine During Acute Hypoxia" Academic Emergency Medicine 7(8):618-624
		Dhainaut, A. et al. (1996) "New Purines and Purine Analogs as Modulators of Multidrug Resistance" J. Med. Chem. 39:4099-4108
		Gao, E. et al. (2001) "Adenosine A1 Receptor Antagonist Prolongs Survival in the Hypoxic Rat" J. Cardiovascular Pharm. 38:384-394
		Ghiardi, G.J. et al. (1999) "The Purine Nucleoside Adenosine in Retinal Ischemia-Reperfusion Injury" Vision Research 39:2519-2535

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 60390-AZ-PCT-US/JPW/GJG/NPD	Serial No. 10/816,329
	INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Applicants: Arlindo L. Castelhano, et al.	
		Filing Date March 31, 2004	Group

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Yes	No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Li, J.M. et al. (1998) "Adenosine A2a Receptors Increase Arterial Endothelial Cell Nitric Oxide" J. Surg. Res. 80:357-364
		Kanda, T. et al. (1998) "Adenosine A2a Receptors Modify Motor Function in MPTP-treated Common Marmosets" Neuroreport 9:2857-2860
		Kanda, T. et al. (2000) "Combined Use of the Adenosine A2a Antagonist KW-6002 with L-DOPA or with Selective D1 or D2 Dopamine Agonists Increases Antiparkinsonian Activity but not Dyskensia in MPTP-Treated Monkeys" Experimental Neurology 162:321-327
		Knutsen, L.J.S. et al. (2001) Curr. Opin. Invest. Drugs 2(5):668-673
		Kopf, S.R. et al. (1999) "Adenosine and Memory Storage: Effect of A1 and A2 Receptor Antagonists" Psychopharmacology 146:214-219
		Montesinos, M.C. et al. (2002) "Adenosine Promotes Wounds Healings and Mediates Angiogenesis in Response to Tissue Injury Via Occupancy of A2a Receptors" American Journal of Pathology 160(6):2009-2018
		Nishiyama, A. (1999) "Adenosine A1 Receptor Antagonists KW-3902 Prevents Hypoxia-Induced Renal Vasoconstriction" J. Pharm. Exp. Ther. 291:988-993
		Nishiyama, A. et al. (2001) "Interactions of Adenosine A1 and A2a Receptors on Renal Microvascular Reactivity" Am. J. Physiol. Renal Physiol. 280:F406-F414
		Phillis, J.W. (1995) "The Effects of Selective A1 and A2a Adenosine Receptor Antagonists on Cerebral Ischemic Injury in the Gerbil" Brain Research 705:79-84
		Taomoto, M. ety al. (2000) "Localization of Adenosine A2 A Receptor in Retinal Development and Oxygen-Induced Retinopathy" Investigative Ophthalmology & Visual Science 41(1):230-243
		Shiozaki, S. et al. (1999) "Actions of Adenosine A2a Receptor Antagonist KW-6002 on Drug-induced Catalepsy and hypokinesia Caused by Reserpine of MPTP" Psychopharmacology 147:90-95
		Svenningsson, P. et al. (1999) "Distribution, Biochemistry and Function of Striatal Adenosine A2a Receptors" Prog. Neurobiol. 59(4):355-396
		Szkotak, A.J. et al. 2001) "Regulation of K+ Current in Human Airway Epithelial Cells by Exogenous and Autocrine Adenosine" Am. J. Physiol. Cell Physiol. 281:C1991-C2002
		Varani, K. et al. (1998) "[^{3}H]-SCH 58261 Labelling of Functional A2a Adenosine Receptors in Human Neutrophil Membranes" Br. J. Pharmacol. 123:1723-1731
		Welch, W.J. (2002) "Adenosine Type 1 Receptor Antagonists in Fluid Retaining Disorders" Expert Opin. Investig. Drugs 11(11):1553-1562
		Zhao, Z. et al. (1996) "Bioactivation of 6,7-Dimethyl-2,4-di-1-pyrrolidinyl-7H-pyrrolo[2,3-d]pyrimidine (U-89843) to Reactive Intermediates that Bind Covalently to Macromolecules and Produce Genotoxicity" Chem. Res. Toxicol. 9:1230-1239

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.